DOI:
10.1016/j.biopsych.2019.01.027

Document Version
Peer reviewed version

NEURAL CORRELATES OF FAILED INHIBITORY CONTROL AS AN EARLY MARKER OF DISORDERED EATING IN ADOLESCENTS

Savani Bartholdy PhD.[1*], Owen G. O'Daly Ph.D.[3], Iain C. Campbell DSc.[1], Tobias Banaschewski M.D., Ph.D.[4], Gareth Barker, PhD[3], Arun L.W. Bokde Ph.D.[5], Uli Bromberg Dipl.-Psych.[6], Christian Büchel M.D.[6], Erin Burke Quinlan Ph.D.[7], Sylvane Desrivières Ph.D.[7], Herta Flor Ph.D.[8,9], Vincent Frouin Ph.D.[10], Hugh Garavan Ph.D.[11], Penny Gowland, PhD.[12], Andreas Heinz M.D., Ph.D.[13], Bernd Ittermann Ph.D.[14], Jean-Luc Martinot M.D., Ph.D.[15], Marie-Laure Paillère Martinot M.D., Ph.D.[16], Frauke Nees Ph.D.[4,8], Dimitri Papadopoulos Orfanos Ph.D.[10], Luise Poustka M.D.[17,18], Sarah Hohmann, M.D.[4], Juliane H. Fröhner Dipl.-Psych.[19], Michael N. Smolka M.D.[19], Henrik Walter M.D., Ph.D.[13], Robert Whelan Ph.D.[20], Gunter Schumann M.D.[7], Ulrike Schmidt M.D., PhD[1,2], IMAGEN Consortium.

[1]Section of Eating Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom

[2]South London & Maudsley NHS Foundation Trust, London, United Kingdom

[3]Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom

[4]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, 68159 Mannheim, Germany

[5]Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin

[6]University Medical Centre Hamburg-Eppendorf, House W34, 3.OG, Martinistr. 52, 20246, Hamburg, Germany

[7]Medical Research Council - Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom

[8]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, Mannheim, Germany

[9]Department of Psychology, School of Social Sciences, University of Mannheim, 68131 Mannheim, Germany

[10]Neurospin, CEA, Université Paris-Saclay, F-91191, Gif-sur-Yvette, France

[11]Departments of Psychiatry and Psychology, University of Vermont, 05405 Burlington, Vermont, USA

[12]Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, Nottingham, United Kingdom

[13]Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité, Universitätsmedizin Berlin, Charitéplatz 1, Berlin, Germany

[14]Physikalisch-Technische Bundesanstalt (PTB), Braunschweig and Berlin, Germany

[15]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry", University Paris Sud - Paris Saclay, University Paris Descartes; and Maison de Solenn, Paris, France

[16]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry", University Paris Sud – Paris Saclay, University Paris Descartes; and AP-HP, Department of Adolescent Psychopathology and Medicine, Maison de Solenn, Cochin Hospital, Paris, France

[17]Clinic for Child and Adolescent Psychiatry, Medical University of Vienna, Währinger Gürtel 18-20, 1090, Vienna, Austria

[18]Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, von-Siebold-Str. 5, 37075, Göttingen, Germany;

[19]Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany

[20]School of Psychology and Global Brain Health Institute, Trinity College Dublin, Ireland

*__Corresponding author:__ Savani Bartholdy

Address: Section of Eating Disorders, Department of Psychological Medicine, Institute of Psychiatry,

Psychology & Neuroscience, King's College London, United Kingdom

Email: savani.bartholdy@kcl.ac.uk

Running title:

Inhibitory control as a biomarker of eating behavior

Keywords:

Inhibitory control, biomarkers, neuroimaging, eating disorders, binge eating, stop signal task

Abstract word count: 250

Main text word count: 3695

Number of tables: 4

Number of figures: 2

Number of supplemental files: 7

ABSTRACT

Background: Binge eating and other forms of disordered eating behavior (DEB) are associated with failed inhibitory control. This study investigated the neural correlates of failed inhibitory control as a potential biomarker for DEB.

Methods: The study used prospective longitudinal data from the European IMAGEN adolescent cohort. Participants completed baseline assessments (questionnaires and a brain scan [functional magnetic resonance imaging, fMRI]) at age 14, and a follow-up assessment (questionnaires) at 16. Self-reported binge eating and/or purging were used to indicate presence of DEB. Neural correlates of failed inhibition were assessed using the stop signal task. Participants were categorized as: Healthy Controls (reported no DEB at both time-points); Maintainers (reported DEB at both time-points); Recoverers (reported DEB at baseline only); and Developers (reported DEB at follow-up only). Forty-three individuals per group with complete scanning data were matched on gender, age, puberty and intelligence (N=172).

Results: At baseline, despite similar task performance, incorrectly responding to stop signals (failed inhibitory control) was associated with greater recruitment of the medial prefrontal cortex and anterior cingulate cortex in the Developers compared to Healthy Controls and Recoverers.

Conclusion: Greater recruitment of medial prefrontal and anterior cingulate regions during failed inhibition accords with abnormal evaluation of errors contributing to DEB development. As this precedes symptom onset, and is evident despite normal task performance, neural responses during failed inhibition may be a useful biomarker of vulnerability for DEB. This study highlights the potential value of prospective neuroimaging studies for identifying markers of illness before the emergence of behavior changes.

INTRODUCTION

Eating disorders (EDs) are characterized by disturbed eating behaviors and extreme concerns about weight and shape. Onset usually occurs during adolescence (1), and early symptomatic behavior is predictive of later development of clinical disorders (2). It would be advantageous to be able to identify vulnerable individuals, however few prospective community-based studies have been conducted to investigate potential behavioral, biological or neural biomarkers of vulnerability.

Adolescence is associated with more impulsive, risky and sensation-seeking behavior compared to childhood and adulthood, attributed at least partly to heterochronous regional brain development (3), e.g., between the maturity of subcortical regions associated with arousal, and immaturity of prefrontal and parietal regions integral to evaluative control over behavior (4). Such developmental events may lead to more impulsive behavior and confer risk of impulsive disordered eating behaviors (DEB). Indeed, neuroimaging studies of inhibitory control in adolescents with EDs have reported altered recruitment of frontostriatal networks implicated in reward processing and self-regulation, though the direction of effect is not consistent (5, 6). Thus, differences in neural functioning related to inhibitory control may contribute to the development of impulsive DEBs (7). It is unclear whether differences in neural activity associated with inhibitory control precede EDs, develop with the illness, or are a consequence of DEB. Prospective longitudinal neuroimaging are necessary to address these questions.

Altered behavioral control has been implicated in ED pathology (8). Many symptoms revolve around the experience of control: e.g., a sense of loss of control during binge eating episodes,

and attempts to regain control over weight or food intake through food restriction/purging, while simultaneously experiencing the inability to stop engaging in restrictive or purging behaviors (9). These are transdiagnostic symptoms that are characteristic across ED diagnoses, with bulimia nervosa (BN) characterized by binge eating and purging, binge eating disorder (BED) by binge eating in the absence of compensatory purging, and the binge-purge subtype of anorexia nervosa (AN) involving binge eating and/or purging. Moreover, EDs (particularly BN and BED) are often comorbid with impulse control disorders (1, 10, 11) such as substance misuse disorders (12), and behavioral dys-control outside of eating contexts is common, suggesting self-regulatory difficulties occur across EDs (6). Additionally, a perceived loss of control (over behaviors, thoughts and/or environment) has been retrospectively identified by patients as contributing to the development of their ED (13-16), and thus may constitute a risk factor for future ED development.

This study used a large multi-national prospective neuroimaging dataset (17) to explore whether neural activity associated with motor inhibitory control can distinguish between individuals reporting DEBs at the time of a brain scan (age 14), those who develop these behaviors later (at age 16) and individuals who do not report/develop these behaviors. Such studies are difficult given the early onset of these disorders and the typical delay in presentation to the clinic. This pioneering project is the first to identify possible neural biomarkers of vulnerability to an ED.

METHODS AND MATERIALS

Participants

Participants were selected from a large European cohort study (the IMAGEN study: 17). A total of 2225 fourteen year olds [T1] were recruited from secondary schools at 8 sites (UK, Ireland, Germany and France). 1607 completed a follow-up assessment at ~16 years old [T2]. Participants were excluded from the IMAGEN study if they had any MRI contraindications, neurological/neurodevelopmental disorders, nutritional/metabolic diseases, certain historical/current medical conditions (e.g., congenital heart defects), IQ<70, or receiving treatment for schizophrenia/bipolar disorder (see 17). Participants in the present study were further excluded if they did not complete the diet, weight and shape element of the Development and Wellbeing Assessment (DAWBA) interview at both time-points, did not provide complete demographic data, or had inadequate/incomplete structural and functional (SST) MRI data).

Eligible participants were categorized into four groups according to self-reported binge eating and purging (DEB): individuals reporting DEB at both time-points ("Maintainers", n=83 [71 girls]), individuals reporting DEB at T1 only ("Recoverers", n=59 [49 girls]), individuals reporting DEB at T2 only ("Developers", n=159, [122 girls]), and individuals reporting no DEB ("Healthy Controls" (HC), n=1265, [567 girls]). Due to differences in group sizes, participants in each category were matched at an individual level to control for potential confounders in neuroimaging analyses of adolescents: age, gender, pubertal stage and intelligence quotient (IQ) (matching procedure outlined in Supplement A). Thus, a total sample of 172 participants comprised of 43 individuals (40 girls) from each group was analyzed

(Supplement B). A description of the endorsed DEBs is provided in supplementary files D and E.

Questionnaires

Disordered eating behavior, anxiety and depression were assessed using the DAWBA, which assesses the presence and frequency of symptoms of several psychiatric disorders (18). The Dieting, Weight and Shape section of the youth version was used to assess DEB: a positive response for either binge eating (eating an objectively large amount of food with associated loss of control; questions 15 and 16) and/or purging (actively getting rid of ingested food by self-induced vomiting or pill use; questions 1c, 18f and 18g) were used to indicate the presence of DEB. Due to insufficient frequency data, only the self-reported presence/absence of DEB was assessed in this study. Probability band scores for anxiety and depression, calculated using information provided by the adolescent, their parent, and their teacher, were used to assess anxiety and depression. Pubertal stage was determined using self-reports on the Pubertal Developmental Scale (PDS; 19). The short form of the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV; 20) was administered to estimate cognitive ability. Lifetime cigarette, alcohol or hash use (i.e., substances known to affect appetite) was assessed at baseline and follow-up using the European School Survey Project on Alcohol and Drugs questionnaire (ESPAD; 21).

Body Mass Index (BMI)

Height and weight were measured at both time-points to calculate BMI (kg/m^2). Standardized BMI *z*-scores were calculated to provide age and sex-adjusted relative weight-for-height assessments (22).

Stop Signal Task

Neural responses to successful and failed inhibitory control were assessed using an fMRI stop signal task (SST). This reactive response inhibition task assesses action cancellation (23), and involves two concurrent tasks: a choice reaction time task ("go trials": 80%, 400 trials) where participants must indicate the direction (left/right) of a presented arrow ("target", 1000ms stimulus duration) using a button-press response, and a stop task where participants must inhibit their motor response ("stop trials": 20%, 87 trials) when an unpredictable stop signal (upwards arrow, shown for 100-300ms) is presented at a variable delay after target onset. Stop trials were infrequent to encourage rapid responding. The delay between the target and stop signal (stop signal delay; SSD) was dynamically adjusted in a stepwise manner (in 50ms increments/decrements, range: 0-900ms, initial delay: 150ms) to ensure participants' stop accuracy converges at approximately 50% correct inhibition. The inter-trial interval was 1800ms. Behavioral dependent variables from this task included the mean SSD, stop accuracy, mean reaction time on correct go trials (mean RT) and the stop signal reaction time (SSRT). SSRT reflects the latency of the stop process (24), calculated by subtracting mean SSD from mean RT (25).

Procedure

Neuroimaging and questionnaire data were obtained from adolescents at T1; follow-up questionnaires were completed online at T2. The DAWBA, PDS and ESPAD were completed on a computer. A researcher administered the WISC-IV, at both time-points.

Ethical approval

Procedures were approved by local ethics committees at each site. Written informed consent from the parents and written assent from the children were obtained prior to participation.

Data analysis

Between-group differences in demographic data and SST measures were explored using one-way ANOVAs. Significant group differences were further assessed using Bonferroni-corrected post-hoc *t*-tests. Square-root transformations were effective in normalizing the positively-skewed mean RT, SSD and post-error slowing data, and reflected square-root transformations were effective in normalizing the negatively-skewed SSRT data. The go accuracy data distribution was strongly negatively-skewed. Non-normally distributed demographic and task-based (go accuracy) data were assessed using non-parametric Kruskal-Wallis tests and Bonferroni-corrected post-hoc Mann-Whitney *U* tests. All tests were two-tailed, with the significance level set at α=0.05.

Structural and functional MRI data were acquired using 3 Tesla MRI scanners of different manufacturers (including General Electric, Siemens, Philips, Bruker). Details of the structural and functional neuroimaging procedures are provided in the supplementary files (supplement C). Image preprocessing was completed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). fMRI data processing included manual origin setting, slice-time correction, realignment and coregistration to the T1-weighted structural scan. A study-specific template was created for normalization using Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL; 26). The resultant flow fields were used to normalize the coregistered data to MNI space (27). Normalized images were smoothed using an 8mm FWHM Gaussian Kernel.

Subject-specific regressors were created using onsets corresponding to the presentation of the go target, and duration corresponded to the latency between onset and response. These were

convolved with the canonical hemodynamic response function to create explanatory variables for the following trials: successful stop (SS) trials, failed stop (FS) trials, successful go (SG) trials, missed trials, incorrect go trials and early stop trials (i.e., responding before the appearance of the stop signal). The high pass filter was set to 128Hz, and potential residual autocorrelation was controlled for using an autoregressive function (AR(1)). Scans were checked manually and excluded if there was visual evidence of excessive motion.

First-level contrasts were generated for the following a priori comparisons: failed>successful inhibition (error with intention to stop: FS>SS), failed stop>successful go (erroneous/unwanted vs. wanted response: FS>SG), and successful stop>successful go (successful inhibition: SS>SG). These were taken forward to group-level random-effects analyses, specifically 3 one-way ANCOVAs exploring the main effect of group followed by post-hoc *t*-tests, and subsequent regression analyses to identify group-by-covariate interactions in the relationships between neural recruitment and behavioral performance measures (transformed SSRT and post-error slowing). Cumulative head motion (sum of volume-to-volume Euclidean distance) and study site (dummy variables) were included as nuisance regressors in the models to control for confounding effects of head movement and site. We explored group differences in neural recruitment and the relationship between neural and behavioral outcomes in three planned group comparisons:

- HC vs. Developers: As neither of these groups reported DEBs at the time of the scan, differences between them in neural activity may be a potential marker of future vulnerability;
- HC vs. Maintainers: This allowed comparison of a group who showed current and prolonged DEB with a healthy group;

- Recoverers vs. Maintainers: Both groups reported DEBs at the time of scan, thus differences in neural activity should permit comparison between individuals displaying transient symptoms from individuals with more prolonged symptoms.

Only results which survive FWE correction at $p<0.05$ at a cluster height threshold of $p<0.001$ will be considered significant.

RESULTS

One-way ANOVAs and Kruskal-Wallis tests confirmed no differences between groups in age ($F(3,168)=1.396$, $p=0.246$), puberty ($\chi^2(3)=1.947$, $p=0.583$) and IQ (Verbal: $F(3,168)=0.926$, $p=0.430$; Performance: $F(3,168)=0.130$, $p=0.942$) (Table 1). Chi-squared analyses revealed no differences between the groups in lifetime use of substances known to affect appetite (all $\chi^2(3) \leq 6.057$, $p \geq 0.109$; Supplement F), except for lifetime hash use at follow-up ($\chi^2(3) = 9.521$, $p=0.023$). No differences were observed in the proportion of individuals reporting binge eating and purging between Recoverers and Maintainers at baseline or between Developers and Maintainers at follow-up (all $U \geq 731.0$, $z \geq -1.938$, $p \geq 0.053$) (Supplement D).

Table 1

Group differences in BMI were present at baseline ($F(3,171)=5.013$, $p=0.002$), driven by lower BMI z-scores in the Developers compared to the Recoverers ($t(84)=-3.203$, $p=0.002$) and Maintainers ($t(84)=-3.311$, $p=0.001$), which survived Bonferroni correction. This was not due to differences in endorsement of food restriction amongst Developers (77%) compared to

either Recoverers (79%) or Maintainers (86%) ($\chi^2(2)=1.080$, $p=0.583$) (Supplement E). BMI *z*-scores were also lower in HCs compared to Recoverers ($t(84)=-2.092$, $p=0.039$) and Maintainers ($t(84)=-2.198$, $p=0.031$), though these findings did not survive Bonferroni correction. A trend towards a difference in anxiety ($\chi^2(3)=6.508$, $p=0.089$) and depression ($\chi^2(3)=7.297$, $p=0.063$) was also seen at baseline, driven by greater anxiety in the Developers compared to HCs, ($U=668.0$, z=-2.536, $p=0.011$), and greater depression in the Maintainer group compared to the Developer group ($U=651.0$, z=-2.579, $p=0.010$). However, these did not survive Bonferroni correction. No other group comparisons were significant at an uncorrected level (all $p>0.053$).

Stop signal task

Stop accuracy tended to converge around 40% accuracy (range: 28.7%-62.1%). One-way ANOVAs did not reveal any differences in behavioral performance between groups (Table 2).

Table 2

A trend towards a main effect of group was observed on the contrast comparing failed stops to successful stops (FS>SS) in the right anterior cingulate cortex (ACC)/medial prefrontal cortex (PFC) (Table 3, Supplement G). No main effect of group was observed on the contrasts comparing failed stops to successful go (FS>SG) or successful stop to successful go trials (SS>SG).

Table 3

Group comparisons were further evaluated using post-hoc *t*-tests. The Developers showed significantly greater recruitment during FS>SS compared to HC in a cluster spanning the ACC bilaterally, and compared to Recoverers in three clusters: the caudate (bilaterally); the right inferior parietal lobe, middle and superior temporal gyrus; and the right superior and middle frontal gyrus (Figure 1, Table 4). No differences were observed between the Maintainers, Recoverers and HCs.

Figure 1

Table 4

Relationship between behavioral and neural performance

When exploring the relationship between neural responses and adaptive error-related behavior (i.e., slowing responses after committing an error on the previous trial), a group by covariate interaction was found between post-error slowing and activation in two clusters during failed compared to successful stop trials (one in the precuneus (bilaterally), and another in the insula, thalamus and STG (bilaterally), left putamen and caudate). The parameter estimates (cluster means) were extracted and plotted for further inspection (Figure 2). They revealed that during FS>SS, post-error slowing positively correlated with activity in the regions seen in HC and Developers, but negatively in Recoverers and Maintainers.

Figure 2

DISCUSSION

This study has prospectively identified potential neural correlates (biomarkers) associated with future onset of DEBs. It focused on inhibitory control, a core element of many models of ED (e.g., 7, 8, 28). When adolescents failed to inhibit their responses, those who developed binge eating/purging at age 16 showed greater recruitment of the anterior cingulate and medial PFC implicated in error processing and inhibitory control (29-32) than those who did not report these behaviors at age 16 (Recoverers and HC), suggesting that increased medial PFC activity during failed inhibitory control precedes symptom development. Thus, elevated recruitment of medial PFC and ACC during failed inhibitory control may be a biomarker for future DEB. Importantly, while behavioral performance did not differ, the observation that group by covariate interactions differed between the groups indicates that the relationship between behavior and neural response is disrupted. Thus, adolescents who later become symptomatic show intact inhibitory control at a behavioral level, but differ in the neural response to failed inhibitory control.

It is surprising that there were no neural differences observed between HCs and Recoverers or Maintainers, given that the Recoverers and Maintainers were endorsing DEBs at the time of scanning. In this study, DEB was classified by self-report. As we did not have sufficient information regarding the frequency of the DEBs assessed, our DEB classification may span a range of symptom severities. It may be that the Recoverers engaged in DEB infrequently and therefore may be more similar to HCs with regards to their overall eating behavior, however this could not be formally assessed. Moreover, it is unknown if participants received treatment between the time-points, i.e., it cannot be ascertained whether “recovery” was spontaneous. Future replications could explore whether neural differences are associated with

differences in severity, and evaluate whether the absence of aberrant neural activity could be a marker of symptom cessation.

An elevated medial PFC response in Developers may reflect differences in several processes/mechanisms during failed inhibition, e.g., less fully developed inhibitory processing (4, 30, 33, 34), poorer behavioral flexibility (33), enhanced error detection (31, 35) or greater recruitment of attentional resources (36): the need to elucidate the role of these regions in behavioral responding has been highlighted (37). Group-by-covariate interactions assessed whether neural recruitment during failed inhibition was differentially associated with behavioral responding between the groups. In HCs, adaptive responding (greater post-error slowing) was associated with greater recruitment of the thalamus, dorsal striatum and insula during failed inhibition. As the striatum has been implicated in reward processing and response selection (38) and the insula in self-regulation and emotional processing (39), this activation pattern may reflect the relationships between recruitment of evaluative (decision-making) systems in response to failures and the subsequent deployment of an adaptive strategy (i.e., post-error slowing). While a similar relationship was observed in Developers with respect to post-error slowing, Maintainers and Recoverers displayed the opposite. Specifically, greater slowing following failure to inhibit was associated with less error-related recruitment in symptomatic individuals: post-error slowing (an adaptive behavioral response strategy) is negatively associated with error responses in individuals who reported DEB at the time of scan, and positively associated in those who were not symptomatic at the time of scan. As similar networks are implicated in risky and affective decision making (40-42) and decision making under uncertainty (43), our findings suggest that while enhanced neural responses to errors in the ACC/medial PFC may be a marker of risk for future DEB, the presence of DEBs is associated with abnormal processing of errors (i.e., there is a disconnect

between error-related brain activity and adaptive behavioral responding (post-error slowing) in symptomatic individuals), although no differences in the ability to respond adaptively was observed (44).

Our data are consistent with models implicating frontostriatal systems in the development/maintenance of EDs (7, 45, 46). In addition, reduced recruitment of midline frontal regions has been reported in studies using the SST in individuals with ANR (47, 48). Importantly, while the directionality of the findings is inconsistent with our data, the same regions are being implicated. It is of note that all previous neuroimaging studies using the SST to assess EDs/DEBs have only assessed individuals with ANR and not those who binge eat/purge, and differed in the contrasts explored (hard/easy vs. failed/successful). Moreover, our study explored the relationship between inhibitory control and transdiagnostic symptoms of EDs, rather than its relationship with a particular ED diagnosis. Thus, the inherent sample-based differences may contribute to the differences in directionality. However, rather than being viewed as opposing findings, this inconsistency may instead support spectrum models of EDs, which propose that EDs lie on a spectrum of inhibitory control with ANR at the over-inhibited extremity and BN and BED at the impulsive extremity (8, 49). Our data, together with those of previous studies in ANR (47, 48), may therefore suggest that this spectrum of inhibitory control may be reflected at a neural level, with ANR associated with reduced recruitment and binge eating/purging associated with increased recruitment of the medial PFC and ACC during error-related processing compared to matched HCs. This may indicate reduced efficiency (greater recruitment for equivalent performance) within the error-processing network in individuals who binge/purge compared to asymptomatic individuals. It may also be the over-engagement of frontal/cingulate regions in those who subsequently develop binge/purge behaviors. Alternatively, these findings could reflect enhanced

processing of errors as a function of augmented attentional processes, consistent with observations of greater sensitivity to rewards and punishment in individuals with EDs who binge and/or purge (50, 51). It would be of interest for future research to discriminate between these hypotheses.

Similar regions have been implicated in studies of adolescents who binge/purge using other executive control tasks, though the directionality of findings has been inconsistent. Lock et al., (5) found that adolescents who reported binge eating and purging (including individuals with a diagnosis of either BN or ANBP) showed greater activity in frontal and midline regions during successful inhibition (compared to successful responding) in a task assessing action restraint (the go/no-go task) compared to HC. In contrast, Marsh et al., (6) found adolescents with BN had reduced neural recruitment of these regions during the Simon task. However, while all these tasks require a rapid button-press response, the Simon task required a response on all trials (i.e., had no stop/no-go trials) and compared reaction time on congruent and incongruent trials. Differences in directionality between these studies may therefore be due to differences in the type of inhibitory control assessed.

There are some considerations regarding the method of participant categorization. Firstly, presence/absence of DEBs were determined by self-report. There is a debate surrounding the optimal method of assessing DEBs in children and adolescents, however, we found participants were forthcoming about their behaviors, with a greater prevalence of DEBs emerging from adolescent compared to parental reports (53). Secondly, participant groups were not random. However, the matching procedure is considered a strength of the study. Given the unequal sample sizes between the groups and the impact of pubertal stage, gender, age and IQ on neural development and neuropsychological performance, participants within

each group were matched at an individual level to reduce the possible influence of these variables while maintaining strong power. Thirdly, data were not collected on medication taken at the time of scan, which could affect inhibitory control (54, 55). Finally, this study is not able to determine the extent to which this potential neural biomarker is specific to the DEBs assessed, or a marker of ED vulnerability or impulsive behavior more generally. However, our findings accord with reports of altered error related brain activity (recruitment and coupling of the dorsal ACC following negative feedback on a probabilistic reversal learning task) in individuals with early stage AN compared to HC in the context of comparable behavioral performance (44). However, Geisler et al., (44) excluded participants who reported regular binge eating. Therefore, although our study differed from Geisler et al. (44) in terms of the fMRI task used and in terms of DEB studied, the findings from these studies suggest that altered error-related neural recruitment may precede observable differences in behavior, and may be a potential biomarker/endophenotype for ED vulnerability more generally.

We propose that impulsivity-related recruitment of medial PFC and ACC is related to core symptoms of EDs and may indicate future development of binge eating and purging. Our findings have implications for biomarker research, as this neural profile predated symptom development, and while behavior could not discriminate the groups before symptom development, this was possible with neuroimaging. Thus, until better behavioral metrics are developed, neuroimaging may continue to be an important tool for identifying markers of psychopathological risk.

REFERENCES

1. Hudson JI, Hiripi E, Pope Jr HG, Kessler RC (2007): The Prevalence and Correlates of Eating Disorders in the National Comorbidity Survey Replication. *Biol Psychiatry*. 61: 348-358.
2. Kotler LA, Cohen P, Davies M, Pine DS, Walsh BT (2001): Longitudinal relationships between childhood, adolescent, and adult eating disorders. *J Am Acad Child Adolesc Psychiatry*. 40: 1434-1440.
3. Romer D (2010): Adolescent risk taking, impulsivity, and brain development: Implications for prevention. *Dev Psychobiol*. 52: 263-276.
4. Casey BJ, Jones RM, Hare TA (2008): The adolescent brain. *Ann N Y Acad Sci*. 1124: 111-126.
5. Lock J, Garrett A, Beenhakker J, Reiss AL (2011): Aberrant brain activation during a response inhibition task in adolescent eating disorder subtypes. *Am J Psychiatry*. 168: 55-64.
6. Marsh R, Horga G, Wang Z, Wang P, Klahr KW, Berner LA, et al. (2011): An fMRI study of self-regulatory control and conflict resolution in adolescents with bulimia nervosa. *Am J Psychiatry*. 168: 1210-1220.
7. Berner LA, Marsh R (2014): Frontostriatal circuits and the development of bulimia nervosa. *Front Behav Neurosci*. 8: 395.
8. Brooks SJ, Rask-Andersen M, Benedict C, Schiöth HB (2012): A debate on current eating disorder diagnoses in light of neurobiological findings: is it time for a spectrum model? *BMC Psychiatry*. 12: 76.
9. American Psychiatric Association (2013): *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub.
10. Fernández-Aranda F, Pinheiro AP, Thornton LM, Berrettini WH, Crow S, Fichter MM, et al. (2008): Impulse control disorders in women with eating disorders. *Psychiatry Res*. 157: 147-157.
11. Nazar BP, Pinna CMdS, Coutinho G, Segenreich D, Duchesne M, Appolinario JC, et al. (2008): Review of literature of attention-deficit/hyperactivity disorder with comorbid eating disorders. *Rev Bras Psiquiatr*. 30: 384-389.

12. Mole T, Irvine M, Worbe Y, Collins P, Mitchell S, Bolton S, et al. (2015): Impulsivity in disorders of food and drug misuse. *Psychol Med*. 45: 771-782.
13. Tozzi F, Sullivan PF, Fear JL, McKenzie J, Bulik CM (2003): Causes and recovery in anorexia nervosa: The patient's perspective. *Int J Eat Disord*. 33: 143-154.
14. Reid M, Burr J, Williams S, Hammersley R (2008): Eating Disorders Patients' Views on Their Disorders and on an Outpatient Service A Qualitative Study. *J Health Psychol*. 13: 956-960.
15. Williams S, Reid M (2010): Understanding the experience of ambivalence in anorexia nervosa: the maintainer's perspective. *Psychol Health*. 25: 551-567.
16. Patching J, Lawler J (2009): Understanding women's experiences of developing an eating disorder and recovering: a life-history approach. *Nurs Inq*. 16: 10-21.
17. Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Büchel C, et al. (2010): The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. *Mol Psychiatry*. 15: 1128-1139.
18. Goodman R, Ford T, Richards H, Gatward R, Meltzer H (2000): The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry*. 41: 645-655.
19. Carskadon MA, Acebo C (1993): A self-administered rating scale for pubertal development. *J Adolesc Health*. 14: 190-195.
20. Wechsler D (2003): Wechsler intelligence scale for children–Fourth Edition (WISC-IV). *San Antonio, TX: The Psychological Corporation*.
21. Hibell B, Bjarnason Þ (1997): *The 1995 ESPAD report: alcohol and other drug use among students in 26 European countries*. Swedish council for information on alcohol and other drugs, CAN.
22. Centre for Disease Control and Prevention (2000): Percentile Data Files with LMS Values.
23. Bartholdy S, Dalton B, O'Daly OG, Campbell IC, Schmidt U (2016): A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. *Neurosci Biobehav Rev*. 64: 35-62.

24. Verbruggen F, Logan GD (2008): Response inhibition in the stop-signal paradigm. *Trends Cogn Sci*. 12: 418-424.
25. Logan GD, Cowan WB (1984): On the ability to inhibit thought and action: A theory of an act of control. *Psychol Rev*. 91: 295.
26. Ashburner J (2007): A fast diffeomorphic image registration algorithm. *Neuroimage*. 38: 95-113.
27. Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, et al. (2001): A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos Trans R Soc Lond B Biol Sci*. 356: 1293-1322.
28. Wierenga CE, Ely A, Bischoff-Grethe A, Bailer UF, Simmons AN, Kaye WH (2014): Are extremes of consumption in eating disorders related to an altered balance between reward and inhibition? *Front Behav Neurosci*. 8: 410.
29. Matthews SC, Simmons AN, Arce E, Paulus MP (2005): Dissociation of inhibition from error processing using a parametric inhibitory task during functional magnetic resonance imaging. *Neuroreport*. 16: 755-760.
30. Durston S, Thomas KM, Yang Y, Uluğ AM, Zimmerman RD, Casey B (2002): A neural basis for the development of inhibitory control. *Dev Sci*. 5: F9-F16.
31. Rubia K, Smith AB, Brammer MJ, Taylor E (2003): Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage*. 20: 351-358.
32. Rubia K, Cubillo A, Smith AB, Woolley J, Heyman I, Brammer MJ (2010): Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive–compulsive disorder. *Hum Brain Mapp*. 31: 287-299.
33. Luna B (2009): Developmental changes in cognitive control through adolescence. *Adv Child Dev Behav*. 37: 233-278.
34. Casey BJ, Giedd JN, Thomas KM (2000): Structural and functional brain development and its relation to cognitive development. *Biol Psychol*. 54: 241-257.

35. Bonini F, Burle B, Liégeois-Chauvel C, Régis J, Chauvel P, Vidal F (2014): Action Monitoring and Medial Frontal Cortex: Leading Role of Supplementary Motor Area. *Science*. 343: 888-891.
36. Scolari M, Seidl-Rathkopf KN, Kastner S (2015): Functions of the human frontoparietal attention network: Evidence from neuroimaging. *Curr Opin Behav Sci*. 1: 32-39.
37. Laubach M, Caetano MS, Narayanan NS (2015): Mistakes were made: Neural mechanisms for the adaptive control of action initiation by the medial prefrontal cortex. *J Physiol Paris*. 109: 104-117.
38. Delgado MR (2007): Reward-Related Responses in the Human Striatum. *Ann N Y Acad Sci*. 1104: 70-88.
39. Ochsner KN, Gross JJ (2008): Cognitive emotion regulation insights from social cognitive and affective neuroscience. *Curr Dir Psychol Sci*. 17: 153-158.
40. Jones CL, Minati L, Harrison NA, Ward J, Critchley HD (2011): Under pressure: response urgency modulates striatal and insula activity during decision-making under risk. *PloS one*. 6: e20942.
41. Ochsner KN, Silvers JA, Buhle JT (2012): Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci*. 1251: E1-E24.
42. Rangel A, Camerer C, Montague PR (2008): A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci*. 9: 545-556.
43. Wu C, Sacchet M, Knutson B (2012): Toward an affective neuroscience account of financial risk taking. *Front Neurosci*. 6: 159.
44. Geisler D, Ritschel F, King JA, Bernardoni F, Seidel M, Boehm I, et al. (2017): Increased anterior cingulate cortex response precedes behavioural adaptation in anorexia nervosa. *Sci Rep*. 7.
45. Marsh R (2009): Dysfunctional frontostriatal control systems in bulimia nervosa. *Future Neurol*. 4: 383-387.

46. O'Hara CB, Schmidt U, Campbell IC (2015): A reward-centred model of anorexia nervosa: A focussed narrative review of the neurological and psychophysiological literature. *Neurosci Biobehav Rev*. 52: 131-152.
47. Oberndorfer TA, Kaye WH, Simmons AN, Strigo IA, Matthews SC (2011): Demand-specific alteration of medial prefrontal cortex response during an inhibition task in recovered anorexic women. *Int J Eat Disord*. 44: 1-8.
48. Wierenga C, Bischoff-Grethe A, Melrose AJ, Grenesko-Stevens E, Irvine Z, Wagner A, et al. (2014): Altered BOLD response during inhibitory and error processing in adolescents with anorexia nervosa. *PloS one*. 9: e92017.
49. Brooks SJ (2016): A debate on working memory and cognitive control: can we learn about the treatment of substance use disorders from the neural correlates of anorexia nervosa? *BMC Psychiatry*. 16: 10.
50. Glashouwer KA, Bloot L, Veenstra EM, Franken IH, de Jong PJ (2014): Heightened sensitivity to punishment and reward in anorexia nervosa. *Appetite*. 75: 97-102.
51. Harrison A, O'Brien N, Lopez C, Treasure J (2010): Sensitivity to reward and punishment in eating disorders. *Psychiatry Res*. 177: 1-11.
52. Bartholdy S, Campbell IC, Schmidt U, O'daly OG (2016): Proactive inhibition: an element of inhibitory control in eating disorders. *Neurosci Biobehav Rev*. 71: 1-6.
53. Bartholdy S, Allen K, Hodsoll J, O'Daly OG, Campbell IC, Banaschewski T, et al. (2017): Identifying disordered eating behaviours in adolescents: how do parent and adolescent reports differ by sex and age? *Eur Child Adolesc Psychiatry*. 1-11.
54. Pietrzak RH, Mollica CM, Maruff P, Snyder PJ (2006): Cognitive effects of immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Neurosci Biobehav Rev*. 30: 1225-1245.
55. Kalanthroff E, Teichert T, Wheaton MG, Kimeldorf MB, Linkovski O, Ahmari SE, et al. (2017): The role of response inhibition in medicated and unmedicated obsessive-compulsive disorder patients: evidence from the stop-signal task. *Depress Anxiety*. 34: 301-306.

ACKNOWLEDGEMENTS

This work received support from the following sources: the European Union-funded FP6 Integrated Project IMAGEN (Reinforcement-related behavior in normal brain function and psychopathology) (LSHM-CT- 2007-037286), the Horizon 2020 funded ERC Advanced Grant 'STRATIFY' (Brain network based stratification of reinforcement-related disorders) (695313), ERANID (Understanding the Interplay between Cultural, Biological and Subjective Factors in Drug Use Pathways) (PR-ST-0416-10004), BRIDGET (JPND: BRain Imaging, cognition Dementia and next generation GEnomics) (MR/N027558/1), the FP7 projects IMAGEMEND(602450; IMAging GEnetics for MENtal Disorders) and MATRICS (603016), the Innovative Medicine Initiative Project EU-AIMS (115300-2), the Medical Research Council Grant 'c-VEDA' (Consortium on Vulnerability to Externalizing Disorders and Addictions) (MR/N000390/1), the Swedish Research Council FORMAS, the Medical Research Council, the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, the Bundesministerium für Bildung und Forschung (BMBF grants 01GS08152; 01EV0711; eMED SysAlc01ZX1311A; Forschungsnetz AERIAL), the Deutsche Forschungsgemeinschaft (DFG grants SM 80/7-1, SM 80/7-2, SFB 940/1). Further support was provided by grants from: ANR (project AF12-NEUR0008-01 - WM2NA, and ANR-12-SAMA-0004), the Fondation de France, the Fondation pour la Recherche Médicale, the Mission Interministérielle de Lutte-contre-les-Drogues-et-les-Conduites-Addictives (MILDECA), the Assistance-Publique-Hôpitaux-de-Paris and INSERM (interface grant), Paris Sud University IDEX 2012; the National Institutes of Health, Science Foundation Ireland (16/ERCD/3797), U.S.A. (Axon, Testosterone and Mental Health during

Adolescence; RO1 MH085772-01A1), and by NIH Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centres of Excellence.

Savani Bartholdy was supported by a PhD studentship from the NIHR Mental Health Biomedical Research Centre (BRC) at South London and Maudsley (SLaM) National Health Service (NHS) Foundation Trust and King's College London (KCL). Iain Campbell and Ulrike Schmidt received salary support from the NIHR Mental Health BRC at SLaM and KCL. Ulrike Schmidt is supported by an NIHR Senior Investigator Award. The views are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

IMAGEN Consortium

Dr Michael Rapp, Charite
Dr. Eric Artiges, INSERM
Sophia Schneider, University of Hamburg
Christine Bach, Central Institute of Mental Health
Prof. Dr. Tomas Paus, University of Toronto
Alexis Barbot, Commissariat à l'Energie Atomique
Prof. Dr. Gareth Barker, King's College London
Dr. Arun Bokde, Trinity College Dublin
Dr. Nora Vetter, Technische Universität Dresden
Prof. Dr. Christian Büchel, University of Hamburg
Dr. Anna Cattrell, King's College London
Patrick Constant, PERTIMM
Prof. Penny Gowland, University of Nottingham
Dr. Hans Crombag, University of Sussex
Katharina Czech, Charite
Dr Jeffrey Dalley, Cambridge University
Benjamin Decideur, Commissariat à l'Energie Atomique
Dr. Dr. Tade Spranger, Deutsches Referenzzentrum für Ethik / Institut of Science and Ethics
Dr. Tamzin Ripley, University of Sussex
Dr. Nadja Heym, University of Nottingham
Prof Herta Flor, Central Institute of Mental Health
Dr. Wolfgang Sommer, Central Institute of Mental Health
Birgit Fuchs, GABO:milliarium mbH & Co. KG
Dr. Jürgen Gallinat, Charite
Dr Hugh Garavan, Trinity College Dublin

Prof. Dr. Rainer Spanagel, Central Institute of Mental Health
Mehri Kaviani, University of Nottingham
Dr. Bert Heinrichs, Deutsches Referenzzentrum für Ethik
Prof. Dr. Andreas Heinz, Charite
Naresh Subramaniam, Cambridge University
Dr Tianye Jia, King's College London
Albrecht Ihlenfeld, PTB
James Ireland, Delosis
Dr. Bernd Ittermann, PTB
Dr Patricia Conrod, King's College London
Prof. Dr. Dr. Tobias Banaschewski, Central Institute of Mental Health
Jennifer Jones, Trinity College Dublin
Dr. Arno Klaassen, Scito
Christophe Lalanne, Commissariat à l'Energie Atomique
Dr Dirk Lanzerath, Deutsches Referenzzentrum für Ethik
Dr. Claire Lawrence, University of Nottingham
Dr. Hervé Lemaitre, INSERM
Dr. Sylvane Desrivieres, King's College London
Catherine Mallik, King's College London
Prof. Dr. Karl Mann, Central Institute of Mental Health
Dr Adam Mar, Cambridge University
Lourdes Martinez-Medina, King's College London
Prof. Dr. Jean-Luc Martinot, INSERM
Eva Mennigen, Technische Universität Dresden
Dr. Fabiana Mesquita de Carvahlo, King's College London
Yannick Schwartz, Commissariat à l'Energie Atomique
Dr. Ruediger Bruehl, PTB
Kathrin Müller, Technische Universität Dresden
Frauke Nees, Central Institute of Mental Health
Charlotte Nymberg, King's College London
Dr. Mark Lathrop, CNG
Prof. Dr. Trevor Robbins, Cambridge University
Dr Zdenka Pausova, University of Toronto
Dr. Dr. Jani Pentilla, INSERM
Francesca Biondo, King's College London
Dr. Jean-Baptiste Poline, Commissariat à l'Energie Atomique
Dr Sarah Hohmann, Central Institute of Mental Health
Dr Luise Poustka, University Medical Centre Göttingen/ Medical University of Vienna
Sabina Millenet, Central Institute of Mental Health
Prof. Dr. Michael Smolka, Technische Universität Dresden
Juliane Fröhner, Technische Universität Dresden
Dr Maren Struve, Central Institute of Mental Health
Prof. Dr. Steve Williams, King's College London
Dr. Thomas Hübner, Technische Universität Dresden
Uli Bromberg, University of Hamburg
Semiha Aydin, PTB
John Rogers, Delosis
Alexander Romanowski, Charite
Dr. Christine Schmäl, Central Institute of Mental Health
Dirk Schmidt, Technische Universität Dresden

Stephan Ripke, Technische Universität Dresden
Dr. Mercedes Arroyo, Cambridge University
Dr. Florian Schubert, PTB
Dr. Yolanda Pena-Oliver, University of Sussex
Mira Fauth-Bühler, FOM Hochschule für Oekonomie & Management/Central Institute of Mental Health
Xavier Mignon, PERTIMM
Dr. Robert Whelan, Trinity College Dublin
Dr. Claudia Speiser, GABO:milliarium mbH & Co. KG
Tahmine Fadai, University of Hamburg
Prof. Dr. Dai Stephens, University of Sussex
Dr. Andreas Ströhle, Charite
Dr. Marie-Laure Paillere, INSERM
Nicole Strache, Charite
David Theobald, Cambridge University
Sarah Jurk, Technische Universität Dresden
Dr. Helene Vulser, INSERM
Ruben Miranda, INSERM
Dr. Juliana Yacubian, University of Hamburg
Vincent Frouin, Commissariat à l'Energie Atomique
Alexander Genauck, Charite
Caroline Parchetka, Charite
Isabel Gemmeke, Charite
Johann Kruschwitz, Charite
Katharina Weiß, Charite
Dr. Henrik Walter, Charité Universitätsmedizin Berlin
Jianfeng Feng, Fudan University/Warwick University
Dimitri Papadopoulos, INSERM
Irina Filippi, INSERM
Alex Ing, King’s College London
Dr. Barbara Ruggeri, King’s College London
Bing Xu, King’s College London
Christine Macare, King’s College London
Dr Congying Chu, King’s College London
Eanna Hanratty, King’s College London
Dr. Erin Burke Quinlan, King’s College London
Dr. Gabriel Robert, King’s College London
Prof. Dr. Gunter Schumann, King’s College London
Dr. Tao Yu, King’s College London
Veronika Ziesch, Technische Universität Dresden
Alicia Stedman, University of Nottingham

DISCLOSURES

Conflicts of interest

Dr. Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Lundbeck, Medice, Novartis, Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships. Dr Barker has received funding for a PhD student and honoraria for teaching on scanner programming courses from General Electric Healthcare; he acts as a consultant for IXICO. Dr Walter received a speaker honorarium from Servier (2014). The other authors report no biomedical financial interests or potential conflicts of interest.

Previous presentation

Early versions of this work along with brief abstracts/summaries has been presented in poster format at the Forum for European Neuroscience Societies in Copenhagen, Denmark (2^{nd}-6^{th} July 2016) and at the European College for Neuropsychopharmacology (ECNP) Junior Scientists Workshop in Nice, France (12^{th}-15^{th} March 2015), and as oral presentations at the ECNP Congress in Amsterdam, the Netherlands (29^{th} August – 1^{st} September 2015) and the Academy for Eating Disorders International Conference on Eating Disorders in San Francisco, USA (5^{th}-7^{th} May 2016).

Table 1. Demographic information for the final matched sample of participants who responded at both time-points.

Time-point	Measure	Group [Mean (SD)]			
		HC	Developers	Recoverers	Maintainers
T1 (age 14 years)					
	Age (years)	14.61 (0.36)	14.49 (0.33)	14.66 (0.44)	14.57 (0.35)
	BMI z-score	0.25 (1.04)	0.07 (0.88)	0.67 (0.82)	0.69 (0.83)
	PDS	16.16 (1.46)	15.89 (2.10)	15.65 (2.94)	16.03 (2.17)
	Verbal IQ	106.88 (13.35)	108.20 (11.24)	108.08 (14.57)	109.35 (13.16)
	Performance IQ	104.53 (15.50)	104.80 (15.07)	105.42 (14.80)	106.44 (13.48)
	Anxiety*	0.38 (0.66)	0.57 (0.98)	0.77 (1.07)	0.91 (1.31)
	Depression*	0.50 (0.62)	0.46 (0.92)	0.88 (1.03)	0.97 (1.03)
T2 (age 16 years)					
	Age (years)	16.46 (0.66)	16.47 (0.52)	16.51 (0.75)	16.60 (0.80)
	BMI z-score	-0.09 (1.10)	0.16 (1.06)	0.58 (1.00)	0.51 (0.99)

* DAWBA probability band scores for an anxiety or depressive disorder.

PDS=Puberty Development Scale.

Table 2. SST behavioral outcome data for the four groups, and statistical comparisons between-groups.

	Group				One-Way ANOVA
Outcome (Mean (SD))	HC	Developers	Recoverers	Maintainers	
Mean RT (ms)	475.99 (83.75)	477.10 (96.19)	456.66 (73.02)	465.87 (81.09)	$F(3,167)=0.527$, $p=0.664$
Go Accuracy (%)	92.8% (8.9%)	89.8% (12.9%)	90.7% (15.1%)	89.9% (11.5%)	$F(3,167)=0.548$, $p=0.650$
Stop Accuracy (%)	42.4% (5.4%)	41.7% (6.0%)	41.5% (4.9%)	44.1% (5.2%)	$F(3,167)=0.673$, $p=0.570$
SSRT	227.47 (101.60)	227.07 (75.85)	242.37 (64.32)	241.73 (108.71)	$F(3,167)=0.606$, $p=0.612$
Mean SSD	248.52 (158.55)	250.03 (146.57)	214.29 (112.13)	224.14 (158.51)	$F(3,167)=2.077$, $p=0.105$
Post-error slowing	31.27 (60.43)	28.42 (47.39)	20.99 (52.88)	16.78 (45.83)	$F(3,167)=0.606$, $p=0.612$

Table 3. Peak coordinates emerging from the trend-wise main effect of group contrast on the one-way ANCOVA comparing neural recruitment between groups during failed relative to successful inhibition, covarying for total head motion and study site.

Peak-level *p*(FWE)	*F*	*z*	*k*	Coordinates of peak voxel (mm)			Hemisphere	Location of cluster peak(s)
				x	y	z		
0.094	9.72	4.36	122	20	42	10	Right	Anterior Cingulate Cortex

Table 4. Peak coordinates of the significant clusters emerging from the post-hoc *t*-tests comparing neural recruitment between groups during failed relative to successful inhibition. A cluster (height) threshold of $p<0.001$ and cluster-wise family-wise error correction was applied (p(FWE)<0.05).

	Cluster-level *p*(FWE)	*k*	Coordinates of cluster peak(s) (mm) x	y	z	Hemisphere	Location of cluster peak(s)
Developers > HC							
	0.013	769	18	39	10	Right	Frontal lobe/Anterior cingulate
			12	33	15	Right	Anterior cingulate
			6	44	12	Right	Anterior cingulate
Developers > Recoverers							
	0.012	792	9	3	15	Right	Caudate
			0	-2	15		
			16	-4	14	Right	Caudate (closest)
	0.015	744	48	-46	32	Right	Supramarginal gyrus, parietal lobe
			58	-57	22	Right	Superior temporal gyrus
			54	-64	26	Right	Middle temporal gyrus
	0.042	543	30	20	38	Right	Frontal lobe (closest: middle frontal gyrus)
			24	15	50	Right	Middle frontal gyrus
			24	26	57	Right	Superior frontal gyrus

Figure 1. Statistical parametric maps resulting from post-hoc *t*-tests exploring regions that were more active during failed inhibition (compared to successful inhibition) in the Developers compared to HCs and the Recoverers (i.e., the groups who were asymptomatic at age 16). A cluster (height) threshold of $p=0.001$ and cluster-wise family-wise error correction was applied ($p(FWE)<0.05$).

Figure 2. Regression models assessing the relationship between fMRI parameter estimates and behavioral data. Graphs plotting the parameter estimates for each cluster emerging from the main effect of group analysis for each regression model, illustrating group differences in parameter estimates from clusters in which there was a relationship between post-error slowing and relative activity during failed stops compared to successful stops (row (A) = bilateral precuneus; row (B) = bilateral insula, STG and left thalamus, putamen and caudate). Three group comparisons were plotted (left to right: HC (blue) vs. Developers (orange); HC (blue) vs. Maintainers (green); Recoverers (purple) vs. Maintainers (green)).